UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

22/JUL/2009

MEMORANDUM

Subject:	Name of Pesticide Product:	TREEVIX™ powered by KIXOR® Herbicide
	EPA File Symbol:	7969-ETA
	DP Barcode:	D352239
	Decision No.:	389171
	Action Code:	R010.0
	PC Code:	118203 BAS 800 H (Saflufenacil)

From: Rick J. Whiting, Biologist
Technical Review Branch (TRB)
Registration Division (7505P)

R. Whiting 7/Hasler Team Leader - Tox

To: Kathryn Montague / Joanne Miller, RM Team 23
Herbicide Branch
Registration Division (7505P)

Applicant: BASF Corporation
Agricultural Products
P.O. Box 13528
Research Triangle Park, NC 27709-3528

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt
118203 BAS 800 H (Saflufenacil) [CAS No. 372137-35-4]	70.0
Inert Ingredient(s):	30.0
Total:	100.0%

ACTION REQUESTED: The Risk Manager requests: "Please review the acute toxicology data for this new Saflufenacil product. This product was delayed due to issues with inert clearance. The inerts have now been cleared and the review can proceed. This is part of a trilateral review on the new a.i. BAS 800 H."

BACKGROUND: BASF Corporation has submitted six acute toxicity studies, a Basic CSF dated December 6, 2007 and a proposed label to support the registration of TREEVIX™ powered by KIXOR® Herbicide (previously named BAS 800 01 H TNV Herbicide), EPA File Symbol 7969-ETA. The acute toxicity studies were conducted at Experimental Toxicology and Ecology and assigned MRID numbers 471282-08 thru -13. The Pest Management Regulatory Agency –Health Canada (PMRA) conducted the primary review of the studies. TRB performed the secondary review and made changes as necessary.

A dermal penetration study, MRID number 47128214, was also included with this action. The primary review of this study was conducted by an Agency contractor, Oak Ridge National Laboratory. TRB performed the secondary review.

COMMENTS AND RECOMMENDATIONS:

1. The six acute toxicity studies have been reviewed and classified as acceptable. The dermal penetration study was reviewed and classified as Unacceptable (Guideline). The study is upgradable pending submission and review of a full description of the study methods or copies of the applicable protocols, the analytical results for the dosing formulations, and clarification of the actual (labeled plus non-labeled) dosages of the active ingredient.

2. The acute toxicity profile for TREEVIX™ Powered by KIXOR® Herbicide, EPA File Symbol 7969-ETA, is as follows:

Acute oral toxicity	III	Acceptable	MRID 47128208
Acute dermal toxicity	III	Acceptable	MRID 47128209
Acute inhalation toxicity	IV	Acceptable	MRID 47128210
Primary eye irritation	III	Acceptable	MRID 47128211
Primary skin irritation	IV	Acceptable	MRID 47128212
Dermal sensitization	Negative	Acceptable	MRID 47128213

3. Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System:

PRODUCT ID #: 007969-000276

PRODUCT NAME: TREEVIX™ Powered by KIXOR® Herbicide

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Harmful if absorbed through skin. Harmful if swallowed. Causes moderate eye irritation. Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves (such as Natural Rubber, Selection Category A). Remove and wash contaminated clothing before reuse. Avoid contact with eyes or clothing. [Wear protective eyewear.]*

*[Protective eyewear may be specified, if appropriate]

First Aid:

If on skin: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

If swallowed: Call a poison control center or doctor immediately for treatment advice. Have person sip a glass of water if able to swallow. Do not induce vomiting unless told to by a poison control center or doctor. Do not give anything to an unconscious person.

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing. Call a poison control center or doctor for treatment advice.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

4. In addition, TRB noted that the registrant has included additional First Aid statements. TRB finds this additional labelling information acceptable.

5. The Basic Formulation CSF (dated December 6, 2007) for the proposed product should also be reviewed and accepted by the TRB Chemistry Team.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: September 15, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Acute Oral Toxicity – Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; brown solid)

CITATION: Gamer, A. and R. Landsiedel (2007) BAS 800 01 H – Acute Oral Toxicity Study in Rats. Report Nos. 10A0320/061117 and BASF Registration Document No. 2007/1020183. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. June 27, 2007. MRID 47128208.

SPONSOR: BASF Corporation, Agricultural Products, PO Box 13528, Research Triangle Park, NC 27709-3528

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47128208), six (three per group) fasted, young adult female Wistar HanRcc:WIST (SPF) rats (age: approximately 8-12 weeks; body weight: 174-190 g; source: RCC Ltd Laboratory Animal Services, Wölferstrase 4, CH-4414 Füllinsdorf, Switzerland) were given a single dose of BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1 as a suspension in water at a dose of 2000 mg/kg bw by gavage and observed for 14 days. Animals were assigned to the test groups noted in Table 1. Following a fast period of ≥16 hours, the rats were given a single dose of BAS 800 01H by oral gavage, then observed daily for 14 days. Individual body weights were recorded shortly before administration, weekly thereafter, and at the end of the study. Survivors were sacrificed by CO_2 and a gross necropsy was performed.

All animals survived and gained weight during the study. Impaired general state, dyspnea, and/or piloerection were observed from all animals starting one hour post dosing with recovery by six hours. No macroscopic pathologic abnormalities were noted at necropsy.

LD_{50} Females > 2000 mg/kg bw

BAS 800 01 H is in EPA Toxicity Category III.

This study is classified as Acceptable. It does satisfy the guideline requirements for an acute oral study (OPPTS 870.1100; OECD 423) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 01H
   Description: *"The test substance was homogeneous by visual inspection".*
   Lot/Batch #: 1625:5
   Purity: 69.9% a.i.
   CAS # TGAI: 372137-35-4

2. **Vehicle and/or positive control:** The vehicle was doubly distilled water. No positive controls.

3. **Test animals:**

Species:	Rat, ♀	
Strain:	Wistar/HansRcc:WIST(SPF)	
Age/weight at dosing:	Age: 8 – 12 weeks; nulliparous and non-pregnant Mean body weights were 175 and 189 g for administration 1 and 2 respectively	
Source:	RCC Ltd Laboratory Animal Services, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland	
Housing:	Singly in Makrolon type III cages.	
Diet:	Kliba-Labordiat (Maus/Ratte Haltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland, *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 -24°C
	Humidity:	30 - 70%
	Air changes:	*"fully air-conditioned rooms"*
	Photoperiod:	12 h dark/ 12 h light
Acclimation period:	At least 5 days before dosing.	

B. STUDY DESIGN and METHODS:

1. **Study dates** - Start: February 23, 2007 End: April 19, 2007

2. **Test substance preparation** – The BAS 800 01H preparation was produced shortly before administration by stirring with a high speed homogenizer (Ultra-Turrax) and/or a magnetic stirrer. The stability of BAS 800 01H in the vehicle was determined indirectly by the concentration control or homogeneity analysis.

3. **Animal assignment and treatment** – Animals were assigned to the test groups noted in Table 1. Following a fast period of ≥16 hours, the rats were given a single dose of BAS 800 01H by oral gavage, then observed daily for 14 days. Individual body weights were recorded shortly before administration, weekly thereafter, and at the end of the study. Survivors were sacrificed by CO_2 and a gross necropsy was performed.

Table 1. Doses, mortality/animals treated

Dose, mg/kg bw	Dosing volume, mL/kg bw	♀ (test 1)	♀ (test 2)	♀ (combined test 1 & 2)
2000	10	0/3	0/3	0/6

4. Statistics – No statistical methods were used for LD_{50} computation, since this was a limit test.

II. RESULTS AND DISCUSSION:

A. Mortality – There were no deaths. The oral LD_{50} for females was >2000 mg/kg bw.

B. Clinical observations – The rats showed impaired general state, dyspnoea and piloerection within 1-5 hours of dosing.

C. Body weight - All animals gained weight during the study.

D. Necropsy - No macroscopic pathologic abnormalities were noted at the end of the study.

E. Authors' conclusions: *"Under the conditions of this study, the median lethal dose of BAS 800 01 H after oral administration was found to be greater than 2000 mg/kg body weight in rats."*

F. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: September 15, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Acute Dermal Toxicity – Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; brown solid)

CITATION: Gamer, A. and R. Landsiedel (2007) BAS 800 01 H – Acute Dermal Toxicity Study in Rats. Report Nos. 11A0320/061126 and BASF Registration Document No. 2007/1020184. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. June 27, 2007. MRID 47128209.

SPONSOR: BASF Corporation, Agricultural Products, PO Box 13528, Research Triangle Park, NC 27709-3528

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47128209), five male and five female young adult Wistar HanRcc:WIST (SPF) rats (age: males: approximately 8-10 weeks and females: approximately 12-14 weeks; body weight: males: 268-281 g and females: 215-219 g; source: RCC Ltd Laboratory Animal Services, Wölferstrase 4, CH-4414 Füllinsdorf, Switzerland) were dermally exposed for 24 hours on an area of approximately 10% of the total body surface area on the clipped dorsal and dorsolateral trunk to 2000 mg/kg bw BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1) as a suspension in water. Animals were assigned to test groups noted in Table 1. Twenty-four hours prior to application of the BAS 800 01H preparation, the fur in the dorsal and dorso-lateral regions of the trunk of the rats was clipped. The BAS 800 01H preparation was applied to the clipped skin area, ~40 cm^2 or at least 10% of the body surface, under a semi-occlusive dressing for 24 hours. After exposure, the dressing was removed and the test skin area was rinsed with warm water. Reactions of the test skin site were assessed 30-60 min after removal of the dressing and then weekly thereafter. The rats were observed for clinical signs of toxicity and mortality daily for 14 days. Individual body weights were recorded shortly before administration, weekly thereafter and at the end of the study. Survivors were sacrificed by CO_2 and a gross necropsy was performed.

All animals survived and gained weight during the study. No systemic clinical signs were noted throughout the study. No dermal irritation was noted at the dose site. No macroscopic pathologic abnormalities were noted at necropsy.

LD_{50} Males > 2000 mg/kg bw
LD_{50} Females > 2000 mg/kg bw
LD_{50} Combined > 2000 mg/kg bw

BAS 800 01 H is in EPA Toxicity Category III.

This study is classified as Acceptable. It does satisfy the guideline requirements for an acute dermal study (OPPTS 870.1200; OECD 402) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 01H
   Description: "*The test substance was homogeneous by visual inspection*".
   Lot/Batch #: 1625:5
   Purity: 69.9% a.i.
   CAS # TGAI: 372137-35-4

2. **Vehicle and/or positive control:** The vehicle was doubly distilled water. No positive controls.

3. **Test animals:**

Species:	Rat
Strain:	Wistar/HansRcc:WIST(SPF)
Age/weight at dosing:	Age: ♂ = 8-10 weeks; ♀ = 12-14 weeks, nulliparous and non-pregnant Weight: ♂ = 266-281, ♀ = 215-219 g
Source:	RCC Ltd Laboratory Animal Services, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland
Housing:	Singly in Makrolon type III cages.
Diet:	Kliba-Labordiat (Maus/Ratte Haltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland, *ad libitum*
Water:	Tap water *ad libitum*
Environmental conditions:	**Temperature:** 20 -24°C **Humidity:** 30 - 70% **Air changes:** "*fully air-conditioned rooms*" **Photoperiod:** 12 h dark/ 12 h light
Acclimation period:	At least 5 days before dosing.

B. STUDY DESIGN and METHODS:

1. **Study dates** - Start: February 23, 2007 End: June 15, 2007

2. **Test substance preparation** – The BAS 800 01H preparation was produced shortly before administration by stirring with a high speed homogenizer (Ultra-Turrax) and/or a magnetic stirrer. The stability of the test substance in the vehicle was determined indirectly by the concentration control or homogeneity analysis.

3. Animal assignment and treatment – Animals were assigned to test groups noted in Table 1. Twenty-four hours prior to application of the BAS 800 01H preparation, the fur in the dorsal and dorso-lateral regions of the trunk of the rats was clipped. The BAS 800 01H preparation was applied to the clipped skin area, ~40 cm^2 or at least 10% of the body surface, under a semi-occlusive dressing for 24 hours. After exposure, the dressing was removed and the test skin area was rinsed with warm water. Reactions of the test skin site were assessed 30-60 min after removal of the dressing and then weekly thereafter. The rats were observed for clinical signs of toxicity and mortality daily for 14 days. Individual body weights were recorded shortly before administration, weekly thereafter and at the end of the study. Survivors were sacrificed by CO_2 and a gross necropsy was performed.

Table 1. Doses, mortality/animals treated

Dose, mg/kg bw	Dosing volume, mL/kg bw	♂	♀	♂♀
2000	2.86	0/5	0/5	0/10

4. Statistics – No statistical methods were used for LD_{50} computation, since this was a limit test.

II. RESULTS AND DISCUSSION:

A. Mortality – There were no deaths. The dermal LD_{50} was >2000 mg/kg bw.

B. Clinical observations – There were no clinical signs of toxicity.

C. Local skin reactions – There were no reaction at the test skin sites.

D. Body weight - All animals gained weight during the study.

E. Necropsy - No macroscopic pathologic abnormalities were noted at the end of the study.

F. Authors' conclusions: *"Under the conditions of this study, the acute dermal median lethal dose (LD_{50}) of BAS 800 01 H after dermal application was found to be greater than 2000 mg/kg body weight in male and female rats."*

G. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: September 15, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Acute Inhalation Toxicity – Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; brown solid)

CITATION: Ma-Hock, L. and R. Landsiedel (2007) BAS 800 01 H – Acute Inhalation Toxicity Study in Wistar Rats. Report Nos. 13I0320/067021and BASF Registration Document No. 2007/1039534. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. November 7, 2007. MRID 47128210.

SPONSOR: BASF Corporation, Agricultural Products, PO Box 13528, Research Triangle Park, NC 27709-3528

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 47128210), five male and five female young adult Wistar HanRcc:WIST(SPF) rats (age: males: 7-8 weeks and females: 11-12 weeks; body weight: males: 218.0-228.7 g and females: 198.5-202.0 g; source: RCC Ltd Laboratory Animal Services, Wölferstasse 4, CH-4414 Füllinsdorf, Switzerland) were exposed by nose-only inhalation to BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1) for 4 hours and 10 minutes at a concentration of 5.0 mg/L. The rats were weighed just before exposure, weekly thereafter and at the end of the observation period. They were checked for overt signs of toxicity or mortality twice a day on workdays and once daily on weekends and on holidays. Survivors at study termination were sacrificed by CO_2 and a necropsy was performed. The MMADs were 1.3 and 1.4 µm and the GSD 4.5 and 3.0 at 30 minutes or later after the beginning of the exposure.

All animals survived and gained weight throughout the study. Increased respiration was noted from all animals starting at the beginning of exposure with recovery by day 1 (the day after exposure). Piloerection was noted on the day of exposure with recovery by day 1. No gross pathological abnormalities were noted in any animal at necropsy.

LC_{50} Males > 5.0 mg/L
LC_{50} Females > 5.0 mg/L
LC_{50} Combined > 5.0 mg/L

Based on the LC_{50}BAS 800 01 H is in EPA Toxicity Category IV.

This study is classified as Acceptable. It does satisfy the guideline requirements for an acute inhalation study (OPPTS 870.1300; OECD 403) in the rat.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 01H
   Description: Solid / brown; stored at room temperature; "*The test substance was homogeneous by visual inspection*".
   Lot/Batch #: 1625:5
   Purity: 69.9% a.i.
   CAS # TGAI: 372137-35-4

2. **Vehicle and/or positive control:** The vehicle was compressed air. No positive controls.

3. **Test animals:**

Species:	Rat	
Strain:	Wistar/HansRcc:WIST(SPF)	
Age/weight at dosing:	Age: ♂ = 7-8 weeks; ♀ = 11-12 weeks, nulliparous and non-pregnant Weight: ♂ = 218.0-228.7, ♀ = 197.8-202.0 g	
Source:	RCC Ltd Laboratory Animal Services, Wölferstrasse 4, CH-4414 Füllinsdorf, Switzerland	
Housing:	Singly in H-Temp (PSU) cages with floor area of 800 cm^2.	
Diet:	Kliba-Labordiat (Maus/Ratte Haltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland, *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 -24°C
	Humidity:	30 - 70%
	Air changes:	*"fully air-conditioned rooms"*
	Photoperiod:	12 h dark/ 12 h light
Acclimation period:	At least 5 days before dosing.	

B. STUDY DESIGN and METHODS:

1. **Study dates** - Start: June 25, 2007 End: October 25, 2007

2. **Test substance preparation** – The test substance was disagglomerated in a mixer under addition of 1% (w/w) of Aerosil 200 before introduction into the dust generator, in order to improve dust formation. A dust aerosol was generated using a dosing-wheel dust generator (Gricke) and compressed air introduced into the inhalation chamber.

3. **Exposure conditions** - The following mean values for exposure parameters were obtained.

Supply air, m^3/h	Exhaust air, m^3/h	Substance flow, g/h	Temperature, °C	Relative Humidity (%)
1.5	1.35	45.0	21.6 ± 0.2	51.3 ± 1.3

4. Animal assignment and treatment – Five male and five female rats were assigned to test groups noted in Table 1. Rats were exposed to BAS 800 01 H by nose only for 4 hours. The rats were weighed just before exposure, weekly thereafter and at the end of the observation period. They were checked for overt signs of toxicity or mortality twice a day on workdays and once daily on weekends and on holidays. Survivors at study termination were sacrificed by CO_2 and a necropsy was performed.

Table 1. Concentrations, exposure conditions, mortality/animals treated

Concentration, mg/L		MMAD, µm	GSD	Particle size distribution	Mortality/ # dead/# tested		
Nominal	Actual			≤8.5 µm = 94.8-97.6 %	♂	♀	♂♀
30	5.0±0.2	1.3 & 1.4	4.5 & 3.0	≤5.5 µm = 89.2-91.4 %	0/5	0/5	0/10

5. Generation of the test atmosphere / chamber description: A head-nose inhalation system INA 20 (glass-steel construction, BASF AG, volume ≈ 55 L) was used. The rats were restrained in glass tubes with their snouts projected into the inhalation chamber. The BAS 800 01H dust was produced in the inhalation system with a dust generator and compressed air.

The exposure system was located inside an exhaust cabin in an air-conditioned laboratory. A supply air flow (compressed air) of 1.5 m^3/h was used. The exhaust airflow was set to 1.35 m^3/h. The lower amount of exhaust air, which was adjusted by means of a separate exhaust air system, achieved a positive pressure inside the exposure system. This ensured that the mixture of BAS 800 01H and air was not diluted with laboratory air in the breathing zones of the animals.

The rats were exposed to the inhalation atmosphere for 4 hours plus equilibration time of the inhalation systems (t_{99} about 10 min.)

Nominal concentration: The nominal concentration was calculated from the amount of BAS 800 01H and the supply air flow.

Gravimetric determination: Pre-weighed filters were placed into the filtration equipment. By means of the vacuum pump metered volumes of the dust were drawn through the filter. For each sample the dust aerosol concentration in mg/L was calculated from the difference between the pre-weight of the filter and the weight of the filter after sampling, with reference to the sample volume of the inhalation atmospheres. Mean and standard deviation were calculated for the concentration from the results of the individual measurements. The mean concentration was corrected for the amount of additive used.

Particle size analysis: Before sampling, the impactor was assembled with pre-weighed glass-fibre collecting discs, and a backup particle filter. The impactor was connected to the vacuum pump and two samples were taken from the breathing zone of the animals starting not earlier than 30 minutes after the beginning of the exposure. The sample volume was 6 L. After sampling the impactor was taken apart. The collecting discs and the backup particle filter were re-weighed. The amounts of material adsorbed to the walls of the impactor and in the sampling probe (wall

losses) were also determined quantitatively. The results from the particle size analysis were not corrected for the additive.

6. Statistics - The LC_{50} was calculated using the binomial test.

II. RESULTS AND DISCUSSION:

A. Mortality – There were no deaths. The inhalation LC_{50} was >5 mg/L (actual concentration).

B. Clinical observations – The rats showed increased respiration and piloerection shortly after exposure. They appeared normal by day 1.

C. Body weight - All animals gained weight during the study.

D. Necropsy - No macroscopic pathologic abnormalities were noted at the end of the study.

E. Authors' conclusions: *"Under the conditions of this study, LC_{50} for male and female rats after dust inhalation was >5.0 mg/L."*

F. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: September 15, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Primary Eye Irritation – Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; brown solid)

CITATION: Remmele, M. and R. Landsiedel (2007) BAS 800 01 H – Acute Eye Irritation in Rabbits. Report Nos. 11H0320/062236 and BASF Registration Document No. 2007/1020186. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. June 27, 2007. MRID 47128211.

SPONSOR: BASF Corporation, Agricultural Products, PO Box 13528, Research Triangle Park, NC 27709-3528

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47128211), 0.1 mL bulk volume (~ 44 mg) of undiluted BAS 800 01 H [69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; pH ~ 6 (undiluted moistened with water)] was instilled into the conjunctival sac of the right eye of one male and two female young adult New Zealand White A 1077 INRA (SPF) rabbits (age: ~ 4 months; source: Centre Lago S.A., 01540 Vonnas, France). Before the beginning of application both eyes of each rabbit were examined for signs of pre-existing irritation. Only rabbits with intact cornea and conjunctiva were used. The test substance, 0.1 mL bulk volume (~44 mg), was applied in a single dose to the conjunctival sac of the right eye. About 24 hours after application the treated eye was rinsed with 3 to 6 mL of hand-warm tap water for 1 to 2 minutes using a syringe with a blunt probe. The left eye remained untreated and served as the negative control. Reactions of the treated eyes were assessed at 1, 24, 48, and 72 hours, and then at weekly intervals. Evaluation and grading of reactions in the eye was based on guidelines similar to those proposed by Draize. All rabbits were checked for clinical signs of toxicity and mortality daily.

No corneal opacity or iritis was noted on any rabbit during the study. Positive conjunctival redness (score 2) was noted on 3/3 rabbits one hour after test material instillation with clearance on two rabbits by 24 hours and on the third rabbit by 72 hours. Positive conjunctival chemosis (score 2) and discharge (score 3) was noted on 1/3 rabbits at one hour with clearance by 24 hours. Injected circumscribed area scleral vessels were noted on all rabbits one and 24 hours after test material instillation and on two rabbits 48 hours after test material instillation. BAS 800 01 H was mildly irritating. The highest maximum mean total score was 10.0, recorded one hour after test material instillation.

In this study, the formulation was mildly irritating. BAS 800 01 H is in EPA Toxicity Category III for primary eye irritation.

This study is classified as Acceptable. It does satisfy the guideline requirements for a primary eye irritation study (OPPTS 870.2400; OECD 405) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 01H
   Description: pH ~6 (undiluted BAS 800 01H moistened with water); "*The test substance was homogeneous by visual inspection*".
   Lot/Batch #: 1625:5
   Purity: 69.9% a.i.
   CAS # TGAI: 372137-35-4

2. **Vehicle and/or positive control:** No vehicle was used.

3. **Test animals:**

Species:	Rabbit; 1♂ + 2♀	
Strain:	New Zealand White A 1077 INRA (SPF)	
Age/weight at dosing:	Age ~ 4 months; body weight ♂ = 3.23, ♀ = 3.08, 3.65 kg	
Source:	Centre Lago S. A., 01540 Vonnas, France	
Housing:	Singly in stainless steel cages.	
Diet:	Kliba-Labordiat (Kaninchen & Meerschweinchenhaltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland; rationed at ~130 g/rabbit/d	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 -24°C
	Humidity:	30 - 70%
	Air changes:	"*fully air-conditioned rooms*"
	Photoperiod:	12 h dark/ 12 h light
Acclimation period:	At least 5 days before dosing.	

1. **Study dates** - Start: February 22, 2007 End: April 27, 2007

2. **Test substance preparation** – The test material was applied undiluted.

3. **Animal assignment and treatment** – One male and two females were used. Before the beginning of application both eyes of each rabbit were examined for signs of pre-existing irritation. Only rabbits with intact cornea and conjunctiva were used. The test substance, 0.1 mL bulk volume (~44 mg), was applied in a single dose to the conjunctival sac of the right eye. About 24 hours after application the treated eye was rinsed with 3 to 6 mL of hand-warm tap water for 1 to 2 minutes using a syringe with a blunt probe. The left eye remained untreated and served as the negative control. Reactions of the treated eyes were assessed at 1, 24, 48, and 72 hours, and then at weekly intervals. Evaluation and grading of reactions in the eye was based on guidelines similar to those proposed by Draize. All rabbits were checked for clinical signs of toxicity and mortality daily.

II. RESULTS AND DISCUSSION:

A. Mortality – There were no deaths.

B. Irritation findings – The cornea or the iris was not affected. The conjunctiva showed slight to moderate redness and chemosis, and slight to severe discharge, mainly during the first hour after application. The maximum irritation scores (MIS) at 1, 24, 48, and 72 h were (maximum = 110) 10, 3.3, 1.3, and 0, respectively. The maximum average score (MAS, mean of scores at 24, 48, and 72 h) was 1.52/110 (computed by Reviewer). In addition, injected scleral vessels in a circumscribed area and circular were noted.

	Number "positive"/Number treated			
	Hours			
Observations	**1**	**24**	**48**	**72**
Corneal Opacity	0/3	0/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3
Conjunctivae:				
Redness*	3/3	1/3	1/3	0/3
Chemosis*	1/3	0/3	0/3	0/3
Discharge	1/3	0/3	0/3	0/3

* Score of 2 or more required to be considered "positive"

C. Authors' conclusions: *"Considering the described ocular reactions as well as the average score for irritation, BAS 800 01 H does not show an eye irritation potential under the test conditions chosen."*

D. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: September 16, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Primary Dermal Irritation – Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; brown solid)

CITATION: Remmele, M. and R. Landsiedel (2007) BAS 800 01 H – Acute Dermal Irritation/Corrosion in Rabbits. Report Nos. 18H0320/062235 and BASF Registration Document No. 2007/1020185. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. June 27, 2007. MRID 47128212.

SPONSOR: BASF Corporation, Agricultural Products, PO Box 13528, Research Triangle Park, NC 27709-3528

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47128212), two male and one female young adult New Zealand White A 1077 INRA (SPF) rabbits (age: 6-10 months; source: Centre Lago S.A., 01540 Vonnas, France) were dermally exposed to 0.5 g of undiluted BAS 800 01 H [69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; pH ~ 6 (undiluted moistened with water)] for 4 hours on the clipped dorsolateral skin. The test material moistened with water was applied on a test patch (2.5 cm x 2.5 cm) and placed on the application site. The animals were observed and irritation was scored at 1, 24, 48, and 72 hours after patch removal.

Well defined erythema (grade 2) was noted on 3/3 rabbits immediately and one hour after patch removal with reduction to very slight erythema (grade 1) by 24 hours and with clearance on two rabbits by 48 hours and on one rabbit by 72 hours.

In this study, the formulation was slightly irritating based on the Primary Irritation Index (PII) of 0.8. BAS 800 01 H is in EPA Toxicity Category IV for primary dermal irritation.

This study is classified as Acceptable. It does satisfy the guideline requirements for a primary dermal irritation study (OPPTS 870.2500; OECD 404) in the rabbit.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 01H
   Description: pH ~6 (undiluted BAS 800 01H moistened with water); "*The test substance was homogeneous by visual inspection*".
   Lot/Batch #: 1625:5
   Purity: 69.9% a.i.
   CAS # TGAI: 372137-35-4

2. **Vehicle and/or positive control:** Doubly distilled water.

3. **Test animals:**

Species:	Rabbit; 2♂ + 1♀
Strain:	New Zealand White A 1077 INRA (SPF)
Age/weight at dosing:	Age 6-10 months; body weight ♂ = 3.79, 4.46 kg; ♀ = 4.14 kg
Source:	Centre Lago S. A., 01540 Vonnas, France
Housing:	Singly in stainless steel cages.
Diet:	Kliba-Labordiat (Kaninchen & Meerschweinchenhaltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland; rationed at ~130 g/rabbit/d
Water:	Tap water *ad libitum*
Environmental conditions:	**Temperature:** 20 -24°C **Humidity:** 30 - 70% **Air changes:** *"fully air-conditioned rooms"* **Photoperiod:** 12 h dark/ 12 h light
Acclimation period:	At least 5 days before dosing.

B. PROCIDURES:

1. **Study dates** - Start: February 22, 2007 End: April 27, 2007

2. **Test substance preparation** – The solid BAS 800 01H was minimally moistened with a suitable amount of doubly distilled water to guarantee skin contact immediately before application.

3. **Animal assignment and treatment** – Two males and one female were used. At least 24 hours before application clipping of the dorsolateral region of the trunk of the rabbits. The test substance, moistened with doubly distilled water, was applied in a single dose to the intact skin. The test patch was secured in position with a semi-occlusive dressing. The dressing and test substance residues were removed at the end of the exposure period of 4 hours with Lutrol® and Lutrol®/water (1:1). Reactions of the test skin sites were assessed at 1, 24, 48, and 72 h. Evaluation and grading of reactions was based on guidelines similar to those of Draize. All rabbits were checked for clinical signs of toxicity and mortality daily.

II. RESULTS AND DISCUSSION:

A. Mortality –There were no deaths.

B. Irritation findings – Well defined erythema (grade 2) was observed in all animals immediately and 1 hour after removal of the patch. There was no evidence of edema. The skin reactions subsided with time and all test skin sites were normal by 48-72 hours. The maximum irritation scores (MIS) at 1, 24, 48, and 72 h were (maximum = 8) 2, 1, 0.3, and 0, respectively. The maximum average score (MAS, mean of scores at 24, 48, and 72 h) was 0.4/8 (computed by Reviewer).

INDIVIDUAL SKIN IRRITATION SCORES

ERYTHEMA/EDEMA

Animal Number	Sex	Hours			
		1	24	48	72
400	M	2/0[a]	1/0	1/0	0/0
374	M	2/0	1/0	0/0	0/0
416	F	2/0	1/0	0/0	0/0
Severity of Irritation – Mean Score		2.0	1.0	0.3	0.0

C. Authors' conclusions: *"Considering the described cutaneous reactions as well as the average score for irritation, BAS 800 01 H does not show a skin irritation potential under the test conditions chosen."*

D. Deficiencies: None.

Primary Reviewer: Steve Wong, Ph.D., PMRA **Date: September 16, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

STUDY TYPE: Dermal Sensitization – guinea pig; OPPTS 870.2600; OECD 406

TEST MATERIAL: BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; brown solid)

CITATION: Remmele M. and R. Landsiedel (2007) BAS 800 01 H – Modified Buehler Test (9 inductions) in Guinea pigs. Report Nos. 33H0320/062237 and BASF Registration Document No. 2007/1020187. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, 67056 Ludwigshafen, Germany. June 27, 2007. MRID 47128213.

SPONSOR: BASF Corporation, Agricultural Products, PO Box 13528, Research Triangle Park, NC 27709-3528

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47128213) with BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1), 30 female young adult HsdPoc:DH guinea pigs (age: 5-8 weeks; body weight: 382-425 g; source: Harlan Winkelmann GmbH, Gartenstrasse 27, 33178 Borchen, Germany) were tested using the modified Buehler Method. Prior to first induction application, the animals were distributed to test and control groups randomly. Twice a week during the induction phase and once before the challenge, the left flank was clipped free of fur at least 15 hours before application. The BAS 800 01H preparation (0.5 g of a 70% in doubly distilled water) was applied to the clipped intact skin under an occlusive dressing for 6 hours. A total of 9 induction applications were carried out (on days 0, 1, 2, 7, 8, 9, 14, 15, 16). Reactions of the test skin sites were assessed 24 hours after the beginning of each application. Evaluation and grading of reactions were based on guidelines similar to those of Draize. Thirteen days after the last induction application, all test and control guinea pigs were challenged with the BAS 800 01H preparation (0.5 g of a 70% in doubly distilled water) which was applied to the right flank in the same manner as induction applications. The challenge application was for 6 hours under an occlusive patch. The challenge skin sites were assessed for reactions 24 and 48 hours after the removal of the challenge patch. All animals were checked for clinical signs of toxicity and mortality daily. Body weights were recorded.

A positive control (reliability check) with a known sensitizer was not included in this study. However, separate studies were performed twice a year in the laboratory. The positive controls with alpha-hexylcinnamaldehyde (85%) showed that the test system was able to detect sensitizing compounds under the laboratory conditions chosen. The results of the most recent positive control studies were included in the Report and verified the validity of the test protocol.

No skin irritation was noted after the 1st to 6th induction application of the 70% BAS 800 01 preparation in doubly distilled water. Grade 1 reaction was observed in 1, 2, and 3 guinea pigs after the 7th, 8th, and 9th induction application, respectively.

The challenge with a 70% BAS 800 01 preparation in doubly distilled water did not cause any skin reactions in test and control animals 24 and 48 hours after removal of the challenge patch.

Based on the results of this study, BAS 800 01 H was not a dermal sensitizer.

This study is classified as Acceptable. It does satisfy the guideline requirements for a dermal sensitization study (OPPTS 870.2600; OECD 406) in the guinea pigs.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test material:** BAS 800 01H
   Description: pH ~6 (undiluted BAS 800 01H moistened with water); "*The test substance was homogeneous by visual inspection*".
   Lot/Batch #: 1625:5
   Purity: 69.9% a.i.
   CAS # TGAI: 372137-35-4

2. **Vehicle and/or positive control:** Doubly distilled water.

3. **Test animals:**

Species:	Guinea pig; ♀	
Strain:	HsdPoc: DH	
Age/weight at dosing:	Age 5-8 months; body weight 382-425 g	
Source:	Harlan Winkelmann GmbH, Gartenstr. 27, 33178 Borchen, Germany	
Housing:	5 per stainless steel wire mesh cage	
Diet:	Kliba-Labordiat (Kaninchen & Meerschweinchenhaltung "GLP"), Provimi Kliba SA, Kaiseraugst, Basel Switzerland; *ad libitum*	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 -24°C
	Humidity:	30 - 70%
	Air changes:	*"fully air-conditioned rooms"*
	Photoperiod:	12 h dark/ 12 h light
Acclimation period:	14 days before dosing.	

B. PROCIDURES:

1. **Study dates** - Start: March 6, 2007 End: May 3, 2007

2. **Test substance preparation** – The BAS 800 01H preparation was produced on a weight per weight basis shortly before applications by stirring with a high speed homogenizer (Ultra-Turrax), a magnetic stirrer, and a spatula. The stability of BAS 800 01H in the vehicle was determined indirectly by the concentration control analysis.

3. Animal assignment and treatment – Prior to first induction application, the animals were distributed to test and control groups randomly. Twice a week during the induction phase and once before the challenge, the left flank was clipped free of fur at least 15 hours before application. The BAS 800 01H preparation (0.5 g of a 70% in doubly distilled water) was applied to the clipped intact skin under an occlusive dressing for 6 hours. A total of 9 induction applications were carried out (on days 0, 1, 2, 7, 8, 9, 14, 15, 16). Reactions of the test skin sites were assessed 24 hours after the beginning of each application. Evaluation and grading of reactions were based on guidelines similar to those of Draize. Thirteen days after the last induction application, all test and control guinea pigs were challenged with the BAS 800 01H preparation (0.5 g of a 70% in doubly distilled water) which was applied to the right flank in the same manner as induction applications. The challenge application was for 6 hours under an occlusive patch. The challenge skin sites were assessed for reactions 24 and 48 hours after the removal of the challenge patch. All animals were checked for clinical signs of toxicity and mortality daily. Body weights were recorded.

A positive control (reliability check) with a known sensitizer was not included in this study. However, separate studies were performed twice a year in the laboratory. The positive controls with alpha-hexylcinnamaldehyde (85%) showed that the test system was able to detect sensitizing compounds under the laboratory conditions chosen. The results of the most recent positive control studies were included in the Report and verified the validity of the test protocol.

II. RESULTS AND DISCUSSION:

A. Mortality and body weight –There were no deaths. All guinea pigs gained weight during the study.

B. Skin reactions – No skin irritation was noted after the 1st to 6th induction application of the 70% BAS 800 01 preparation in doubly distilled water. Grade 1 reaction was observed in 1, 2, and 3 guinea pigs after the 7th, 8th, and 9th induction application, respectively.

The challenge with a 70% BAS 800 01 preparation in doubly distilled water did not cause any skin reactions in test and control animals 24 and 48 hours after removal of the challenge patch.

C. Authors' conclusions: *"... the results of this study show that BAS 800 01 H does not have a sensitizing effect on the skin of the guinea pig in the Modified BUEHLER Test under the test conditions chosen."*

D. Deficiencies: None.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** DP352239
2. **PC CODE:** 118203
3. **CURRENT DATE:** 22/JUL/2009
4. **TEST MATERIAL:** BAS 800 01 H (69.9% BAS 800 H; Batch No. 1625:5, Test Substance No. 06/0320-1; brown solid)

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Experimental Toxicology & Ecology 10A0320/061117 / June 27, 2007	47128208	LD_{50} > 2000 mg/kg (females)	III	A
Acute dermal toxicity / rat Experimental Toxicology & Ecology 11A0320/061126 / June 27, 2007	47128209	LD_{50} > 2000 mg/kg (males and females)	III	A
Acute inhalation toxicity / rat Experimental Toxicology & Ecology 13I0320/067021 / November 7, 2007	47128210	LC_{50} > 5.0 mg/L (males and females)	IV	A
Primary eye irritation / rabbit Experimental Toxicology & Ecology 11H0320/062236 / June 27, 2007	47128211	Mildly irritating	III	A
Primary dermal irritation / rabbit Experimental Toxicology & Ecology 18H0320/062235 / June 27, 2007	47128212	Slightly irritating	IV	A
Dermal sensitization / guinea pig Experimental Toxicology & Ecology 33H0320/062237 / June 27, 2007	47128213	Not sensitizing	---	A

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable, W = Waived

DATA EVALUATION RECORD

BENZAMIDE, 2-CHLORO
OPPTS 870.7600
STUDY TYPE: *In Vivo* DERMAL ABSORPTION - RAT
MRID 47128214

Prepared for

Registration Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Prepared by

Toxicology and Hazard Assessment Group
Environmental Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Task Order No. 1-26

Primary Reviewer:
Donna L. Fefee, D.V.M.

Signature: Robert H. Ross for D. L. Fefee
Date: JUL 10 2008

Secondary Reviewers:
H. Tim Borges, Ph.D., MT(ASCP), D.A.B.T.

Signature: Tim Borges
Date: JUL 10 2008

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: JUL 10 2008

Quality Assurance:
Kim Slusher, M.S.

Signature: Kimberly G. Slusher
Date: JUL 10 2008

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of

Primary Reviewer: Donna L. Fefee, D.V.M, ORNL **Date: July 1, 2008**
Secondary Reviewer: Rick Whiting, EPA
Risk Manager (EPA): 23

DATA EVALUATION RECORD

STUDY TYPE: Rodent *In Vivo* Dermal Penetration Study - Rat; OPPTS 870.7600 [§85-2]; OECD none.

PC CODE: 118203 **DP BARCODE:** 352239

TEST MATERIAL (PURITY): ^{14}C-BAS 800 H (Benzamide, 2-chloro; 93.3% a.i.; Lot #825-1401) and BAS 800 02 H (12.0% non-labeled BAS 800 H; Batch #1613-91)

SYNONYMS: N'-[2-chloro-4-fluoror-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoly]-N-isopropyl-N-methylsulfamide-[phenyl-U-C14]

CITATION: Fabian, E. and R. Landsiedel (2007) Study on the dermal penetration of 14C-BAS 800 H in BAS 800 02 H in rats. Experimental Toxicology and Ecology, BASF Aktiengesellschaft, Ludwigshafen/Rhein, Germany. Laboratory report number 01B0627/046022, December 18, 2007. MRID 47128214. Unpublished.

SPONSOR: BASF Corporation, Agricultural Products, Research Triangle Park, North Carolina

EXECUTIVE SUMMARY: In a dermal penetration study (MRID47128214) ^{14}C-BAS 800 H (Benzamide, 2-chloro; 93.3% a.i.; Lot #825-1401) in BAS 800 02 H (12.0% non-labeled BAS 800 H; Batch #1613-91) was administered to four male Crl:WI (Han) rats/dose/sacrifice interval at nominal dose levels of 0.0117, 0.1172, and 1.1723 mg ai/cm^2 skin (actual doses, as calculated by reviewer: 0.0221, 0.1290, and 1.1909 mg ai/cm2 skin, respectively). Dosing formulations were applied to intact, 10-cm^2, clipped dose sites on the dorsum for a 10-hour exposure duration, and animals were sacrificed at 10, 24, 72, and 120 hours after application. Application sites were washed at the conclusion of the 10-hour exposure, with a second wash prior to sacrifice if appropriate.

Skin irritation/corrosion was observed on the application sites of the sixteen animals that were given the nominal 1.1723 mg/cm^2 dose; data from these animals should not be used to determine the percent dermal absorption because the dermal barrier was compromised. Recovery of the applied dose (mass balance) was acceptable, with group means for the low- and mid-dose groups ranging from 92.00% to 104.07%. Results were not adjusted for recoveries or values below the limit of detection.

A range of 3.08% to 11.57% of the applied dose was retained at the application sites of the low- and mid-dose groups. Estimates of dermal absorption were based on the sum of residues found in the urine, feces, blood cells, plasma, carcass, and cage wash, and 2.78% to 8.57% of the applied dose was absorbed. At both dose levels, the majority of the recovered absorbed dose was in the carcass at 10 and 24 hours and in the feces at 72 and 120 hours. The data suggest that the test material remaining in the skin of the application site and the surrounding skin at 10 hours

may have moved into other matrices during the remainder of the study; however, the increases in the percentage absorbed and the correlated decreases in the percentages in the application site and surrounding skin did not show clear linear differences over time and the magnitude of the differences over time and between groups may fall within the margin of error for the analytical method.

The data from the low- and mid-dose group indicated that the test material was not readily absorbed, was not retained to a significant extent, and was excreted at roughly a two to one ratio in the feces and urine. The proportion of radioactivity found in the feces indicates that the test material is metabolized in the liver, at least to some extent. Saturation of the absorption process did not occur.

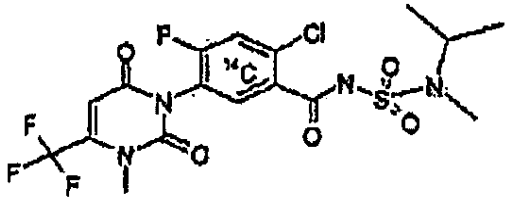
This study in the rat is **Unacceptable (Guideline)** and **does not satisfy** the guideline requirement for a dermal penetration study (870.7600) in rats. The study is upgradable pending submission and review of a full description of the study methods or copies of the applicable protocols, the analytical results for the dosing formulations, and clarification of the actual (labeled plus non-labeled) dosages of the active ingredient.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: ^{14}C-BAS 800 H

Description:	None provided
Batch #:	825-1401
Purity:	93.3% (HPLC)
Compound stability:	Not provided
CAS # for TGAI:	372137-35-4 (non-radiolabelled)
Structure:	
Vehicle/Solvent used:	BAS 800 02 H [12.0% BAS 800 H]; Batch #1613-91; Density: 0.9769 g/mL
Radiolabelling:	Phenyl-U-C14; see above for structure
Specific Activity:	5.11 MBq/mg (LSC)
Radiochemical Purity:	98.8% (RHPLC)
Source:	Study sponsor
Other comments:	The 14C-BAS 800 H was stored under refrigeration and in the dark. The BAS 800 02 H was stored under ambient conditions.

2. **Relevance of test material to proposed formulation(s):** Except for the concentration of the active ingredient, the individual formulation components of the vehicle (i.e. the BAS 800 02 H formulation) were not provided; however, the vehicle *is* the end use product itself. The "formulation concentrate" that was applied to the animals differed from the proposed formulation in containing a larger amount of the active ingredient due to the addition of radiolabelled active ingredient. The relevance of testing a higher concentration than would occur under any field exposure conditions is unclear.

3. **Test animals:**

Species:	Rat	
Strain:	Crl:WI (Han)	
Age/weight at study initiation:	Males: 6-12 weeks old/280-330 g	
Source:	Charles River Laboratories, Sulzfeld, Germany	
Housing:	During acclimation: in pairs in type III Macrolon cages; during experiments: individually in Metabowl type, all-glass metabolism cages (Jencons, Leighton Buzzard, UK)	
Diet:	Kliba lab diet for rat-mouse (pelletized or meal), *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	20-24°C
	Humidity:	30-70%
	Air changes:	not reported
	Photoperiod:	reported as "natural day/night rhythm"
Acclimation period:	At least three days	

B. STUDY DESIGN:

1. Dose:

TABLE 1. Dosing

Nominal dose level (mg/cm^2)	Amount non-labeled compound in 100 µL dosing solution (mg)[a]	Specific activity (dpm/µg)	Mean radioact. dose (MBq/animal)[b]	Actual dose		
				Radiolabeled (mg/animal)[c]	Non-labeled (mg/animal)[b]	Total dose (mg/cm^2)[d]
1.1723	11.723	3599.8	0.708	0.1387	11.770	1.1909
0.1172	1.1723	28146.4	0.555	0.1086	1.1810	0.1290
0.0117	0.1172	115708.4	0.310	0.0607	0.1598	0.0221

Data taken from pp. 17, 28-39, and 43, MRID 47128214.

[a] Calculated by reviewer using reported density and % a.i. of the "vehicle" (BAS 800 02 H).

[b] Calculated by reviewer as the mean of the group mean values at each time point.

[c] Calculated by reviewer as the mean radioact. dose per animal/the specific activity of the radiolabeled test material (or 5.11 MBq/mg).

[d] Calculated by reviewer as (the radiolabeled dose per animal + the non-labeled dose per animal)/10 cm^2.

Rationale: Dose selection was based on spanning a broad range of potential exposure during use. The highest dose level was the formula concentrate [the formulation containing non-radiolabeled test material at a 12.0% (w/w) concentration, with added radiolabeled test material], and the lower dose levels were spaced at log intervals.

Nominal doses: 0.0117, 0.1172, and 1.1723 mg ai/cm^2 skin with intended radioactivity of approximately 0.3, 0.6, and 0.7 MBq/animal, respectively.

Actual doses: 0.0221, 0.1290, and 1.1909 mg ai/cm^2 skin. [See Table 1 for details.]

Dose volume: 100 µL/10 cm^2 skin.

Duration of exposures (time from dose to skin wash): Ten hours.

Termination periods (time from dose to sacrifice): Four rats per dose level were sacrificed 10, 24, 72, and 120 hours after initial application of the test material.

Number of animals/group: There were four animals per dose per exposure duration.

2. **Animal preparation:** Twenty-four hours before dosing, the dorsum of each animal was partially clipped, and the clipped area was cleaned with acetone. Only animals with undamaged skin at the time of dosing were used. On the day of dosing, a glass ring spacer was affixed to the skin of the dorsum with tissue glue.

3. **Dose preparation, administration and quantification:**

   Preparation: Dose suspensions were prepared by making a stock solution of the radiolabeled test item in acetone and evaporating an appropriate amount of the stock solution to dryness, after which the dried residue was "taken up in the formulation" to attain the formulation concentrate. The 1/10 (v/v) and 1/100 (v/v) aqueous dilutions were prepared by preparing an appropriate amount of the formulation concentrate, as above, and combining it with an appropriate amount of tap water. All formulations were stirred and sonicated. The study authors did not state when the formulations were prepared in relation to dosing.

   Application: A 100 µL volume of the appropriate preparation was applied to the application site (approximately 10 cm^2) using a pipette. To protect the application site, a permeable gauze dressing was placed over the spacer and further covered by a semi-occlusive adhesive bandage. The treated animals were placed in Metabowl type metabolism cages (Jencons, Leighton Buzzard, UK) equipped with urine and feces collection. Carbon dioxide was not collected.

   Quantification: Pre-dose and post-dose samples of the formulations were analyzed to confirm radioactivity levels and homogeneity. The pipette used to apply the dose was weighed before and after application. None of these data were included in the study report.

4. **Skin wash (pre-sacrifice):** Ten hours after application, the gauze and bandages were removed, and the skin of the animals was washed with a mild soap solution. For animals not designated to be sacrificed at this time point, fresh gauze and bandages were applied, and the skin was washed a second time immediately prior to sacrifice at 24, 72, or 120 hours after application. Details of the washing procedure were not provided. Washing solutions and the gauze and bandage were retained for radioactivity determination.

5. **Sample collection:** Urine and feces were collected from all rats of all dose groups at 10 hours after application of the test material, and, where appropriate, excreta were also collected 24 hours after application and at 24-hour intervals up to 120 hours after application. Animals were sacrificed according to schedule (at 10, 24, 72, or 120 hours after application), and the following samples were collected for total radioactivity determination: exreta (urine and feces), blood (blood cells and plasma), the application site, skin surrounding the application site, the remaining carcass, the cage wash, and the glass ring. No details were provided concerning the euthanasia or sample collection methods. Individual organs and other tissues were not analyzed separately.

6. **Sample preparation and analysis:** All samples were weighed. The study authors stated that "conventional methods described in standard operating procedures" were used to prepare the samples of biological material for analysis. The standard operating procedures were not provided, and aside from a brief mention that some (unspecified) samples were freeze dried, no further details were available.

Liquid scintillation counting was used to measure radioactivity. Total amounts of radioactivity in samples were reported as a percentage of the total dose administered and/or as equivalents of test material per tissue weight. The specific equipment used was not described, and the study report did not mention validation of the radioanalysis procedures or establishment of the limits of detection.

II. RESULTS:

A. SIGNS AND SYMPTOMS OF TOXICITY: Skin irritation/corrosion was observed on the application sites of the sixteen animals that were given the nominal 1.1723 mg/cm^2 doses. No other abnormal clinical signs were reported.

B. SUMMARY TABLES:

TABLE 2: Recovery of radioactivity (% applied dose) in each matrix following application of ^{14}C-BAS 800 H to male rats at a nominal dose of 1.1723 mg/cm^2 with skin wash at 10 hours and prior to termination [a]

Matrix	Number of hours post application			
	10 h	24 h	72 hr	120 h
Urine	10.60	19.66	22.78	23.41
Feces	0.08	6.96	45.88	56.48
Blood cells	0.87	0.19	0.01	0.00
Plasma	1.26	0.35	0.01	0.01
Carcass	52.84	39.45	5.48	0.65
Cage Wash	0.76	1.42	1.05	0.46
Percentage Absorbed	66.41	68.04	75.21	81.01
Application site	3.63	2.52	2.73	1.73
Surrounding skin	5.62	4.76	2.14	1.54
Protective cover	21.14	24.16	29.86	26.00
Skin wash	2.38	4.56	3.05	4.91
Second skin wash	N/a [b]	0.25	0.15	0.02
Total Recovery	99.18	104.28	113.14	115.20

[a] Data taken from Table 1, p. 27, MRID 47128214. Mean of 4 animals/group.

[b] N/a = not applicable.

TABLE 3: Recovery of radioactivity (% applied dose) in each matrix following application of ^{14}C-BAS 800 H to male rats at a nominal dose of 0.1172 mg/cm^2 with skin wash at 10 hours and prior to termination [a]

Matrix	Number of hours post application			
	10 hr	24 hr	72 hr	120 hr
Urine	0.07	0.38	1.44	0.66
Feces	0.02	0.62	5.82	2.32
Blood cells	0.03	0.03	0.01	0.00
Plasma	0.08	0.09	0.01	0.00
Carcass	2.56	2.78	1.20	0.32
Cage Wash	0.03	0.06	0.09	0.06
Percentage Absorbed	2.78	3.96	8.57	3.36
Application site	5.44	3.97	3.73	3.08
Surrounding skin	0.43	0.17	0.15	0.21
Protective cover	1.22	6.56	5.79	3.52
Skin wash	90.98	85.66	82.17	92.67
Second skin wash	N/a [b]	0.76	0.28	0.29
Total Recovery	100.85	101.07	100.68	103.12

[a] Data taken from Table 1, p. 27, MRID 47128214. Mean of 4 animals/group.

[b] N/a = not applicable.

TABLE 4: Recovery of radioactivity (% applied dose) in each matrix following application of ^{14}C-BAS 800 H to male rats at a nominal dose of 0.0117 mg/cm^2 with skin wash at 10 hours and prior to termination [a]

Matrix	Number of hours post application			
	10 hr	24 hr	72 hr	120 hr
Urine	0.07	0.49	0.51	1.20
Feces	0.01	0.39	2.17	3.88
Blood cells	0.06	0.03	0.01	0.01
Plasma	0.13	0.04	0.01	0.01
Carcass	3.09	3.77	1.23	0.73
Cage Wash	0.04	0.09	0.09	0.10
Percentage Absorbed	3.39	4.80	4.01	5.94
Application site	11.57	6.36	6.84	5.59
Surrounding skin	0.10	0.07	0.10	0.04
Protective cover	3.11	7.70	8.26	2.73
Skin wash	73.83	83.72	77.04	85.89
Second skin wash	N/a [b]	1.42	1.29	0.86
Total Recovery	92.00	104.07	97.52	101.04

[a] Data taken from Table 1, p. 27, MRID 47128214. Mean of 4 animals/group.

[b] N/a = not applicable.

C. TOTAL ABSORBED DOSE:

Results of the analyses are summarized in Tables 2, 3, and 4. The increased absorption at the highest dose level is due to increased permeability resulting from direct dermal toxicity, and these data will not be discussed further. Recovery of the applied dose (mass balance) was acceptable, with group means for the low- and mid-dose groups ranging from 92.00% to 104.07%. Results were not adjusted for incomplete recovery of the applied dose (or recovery of an amount greater than the applied dose), and there was no adjustment for values below the limit of detection.

A range of 3.08% to 11.57% of the applied dose was retained at the application sites of the low- and mid-dose groups. Estimates of dermal absorption were based on the sum of residues found in the urine, feces, blood cells, plasma, carcass, and cage wash, and 2.78% to 8.57% of the applied dose was absorbed. At both dose levels, the majority of the recovered absorbed dose was in the carcass at 10 and 24 hours and in the feces at 72 and 120 hours. The data suggest that the test material remaining in the skin of the application site and the surrounding skin at 10 hours may have moved into other matrices during the remainder of the study; however, the increases in the percentage absorbed and the correlated decreases in the percentages in the application site and surrounding skin did not show clear linear differences over time and the magnitude of the differences over time and between groups may fall within the margin of error for the analytical method.

The data from the low- and mid-dose group indicated that the test material was not readily absorbed, was not retained to a significant extent, and was excreted at roughly a two to one ratio in the feces and urine. The proportion of radioactivity found in the feces indications that the test material is metabolized in the liver, at least to some extent. Saturation of the absorption process did not occur.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The study author concluded that following single dermal administration of ^{14}C-BAS 800 H for ten hours as a formulation concentrate (high dose), dermal absorption ranged from 66.41% of the applied dose at the end of the exposure period to 81.01% at 120 hours after initial administration. The study author also concluded that in the mid- and low-dose groups, dermal absorption ranged from 2.78-3.39% at the conclusion of the exposure period up to 5.94-8.57% during the remainder of the study. The study author also noted that approximately two thirds of the high dose material remaining in the skin at ten hours was absorbed during the remainder of the five-day observation period, whereas about half of this material was absorbed following the mid- and low-dose administrations.

B. REVIEWER COMMENTS: The dose selection for the high-dose group was not appropriate because of skin damage, and further analysis of the results from this group is also inappropriate. The reviewer generally agrees with the remainder of the investigators' conclusions.

C. STUDY DEFICIENCIES: The occurrence of skin irritation/corrosion in all of the animals treated at the highest dose level is considered a serious deficiency. OPPTS 870.7600 states that compounds that are caustic or are dermal irritants should be tested only at doses that do not show such effects.

The analytical results for the dosing formulations were not reported.

The study methods were not described in sufficient detail. In particular, the end concentrations of radiolabeled plus non-labeled active ingredient in the dosing formulations were not clearly described. The study report *seemed* to only include the values for the non-labeled active ingredient, thus necessitating calculation of the applied amount of radiolabeled active ingredient by the reviewer. However, it is also possible that the combined labeled plus non-labeled dose *was* reported but that the entire 100 µL dose volume was not applied for some reason. The actual (labeled plus non-labeled) dosages of the active ingredient need to be clarified.